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| EXAMINER | |
|---|---|
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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/607,571 | BATYCKY ET AL. | |
| | Examiner | Art Unit | |
| | JAMES H. ALSTRUM ACEVEDO | 1616 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *27 November 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *140-144, 146-150, 153, and 156-173* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *140-144,146-150,153 and 156-173* is/are rejected.

7)☒ Claim(s) *161-162* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

## DETAILED ACTION

**Claims 140-144, 146-150, 153, and 156-173 are pending.** Applicants previously cancelled claims 1-139, 145, 151-152, and 154-155. Receipt and consideration of Applicants' arguments/remarks submitted on November 27, 2007 are acknowledged. Any rejections previously of record that are not explicitly maintained herein have been withdrawn per Applicants' persuasive arguments.

### *Priority*

Clarification is kindly requested regarding Applicants' priority claims. On November 28, 2003 Applicants submitted a preliminary amendment to the specification (shown below), which indicated that the instant application claims benefit of U.S. provisional application No. 60/425,349 and is ***related to*** U.S. provisional application nos. 60/393,007 and 60/393,716. It is unclear whether the phrase "related to" is meant to claim benefit of provisional application nos. 60/393,007 and 60/393,716. Appropriate clarification and amendment, as appropriate, is respectfully requested.

**Amendments to the Specification:**

Please replace the paragraph at page 1, lines 3 through 7 with the following amended paragraph:

This application claims the benefit of U.S. Provisional Application No. ~~60/425,349~~ 60/425,349, filed November 8, 2002. This provisional application is related to U.S. Provisional Application No. 60/393,007, filed on June 28, 2002, and U.S. Provisional Application No. 60/393,716, filed on July 2, 2002. The entire teachings of the above application(s) are incorporated herein by reference.

***Claim Rejections - 35 USC § 112***

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

**Claims 140-144, 146-150, 153, 156-160, 163-171, and 173 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.**

Independent claims 140 and 173 are indefinite, because these claims claim a method of treating a person in need of epinephrine comprising…administration of epinephrine… Applicants are not claiming a method of administration, but a method of treatment. It is unclear what condition or disease is being treated, due to the circular description of the claimed method of treatment. Appropriate clarification and correction are required.

The remaining claims are rejected as depending from a rejected claim.

***Claim Objections***

**Claims 161-162 are objected** for depending from a rejected claim.

***Claim Rejections - 35 USC § 103***

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.

3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

The rejection of claims 140-144, 153, and 156-160 under 35 U.S.C. 103(a) as being unpatentable over Tarara et al. (US 2005/0074498) in view of Slutsky et al. (U.S. Patent No. 6,102,036) **is maintained** for the reasons of record, which have been restated below for Applicants' convenience.

***Applicant Claims***

Applicants claim a method for treating a patient in need of epinephrine comprising administering spray-dried particles from a dry powder inhaler to the respiratory system of a patient in a single, breath-activated step, the particles comprising (a) epinephrine or a salt thereof and, (b) at least one pharmaceutically acceptable excipient, wherein the particles administered to the patient comprise at least about 50 micrograms of epinephrine, have a tap density of less than 0.4 g/cm3, and possess a fine particle fraction of less than 5.6 microns of at least about 45 percent.

***Determination of the Scope and Content of the Prior Art (MPEP §2141.01)***

Tarara discloses engineered particles that may be used for the **delivery of a bioactive agent to the respiratory tract of a patient**. The particles may be used in the form of dry powders or in the form of stabilized dispersions comprising a nonaqueous continuous phase. In particularly preferred embodiments the particles may be used **in conjunction with an inhalation** device such as a dry powder inhaler, metered dose inhaler or a nebulizer (abstract).

Tarara discloses that the disclosed powders may comprise the selected agent or bioactive agent, or agents as the sole structural component of the perforated microstructures. Conversely, the perforated microstructures may comprise **one or more components (i.e. structural materials, surfactants, excipients**, etc.) in addition to the incorporated agent [0040].

Tarara discloses that his invented preparations provide highly flowable dry powders that can be efficiently aerosolized, uniformly delivered, and penetrate deeply in the lung or nasal passages [0050]. Any bioactive agents that may be formulated in the perforated microstructures are expressly held to be within the scope of pharmaceutical preparations taught by Tarara, including **bronchodilators and steroids** [0069]. Exemplary medicaments of biologically active agents suitable for used in Tarara's formulations include bronchodilators, such as **adrenaline** [0070]. Adrenaline and epinephrine are synonyms for the same compound.

In preferred embodiments, Tarara's compositions are comprised of microstructures formed by **spray drying** [0075]. The **mean aerodynamic diameter of the perforated microstructures is preferably less than about 5 microns, and in particularly preferred embodiments less than 2 microns**. These particle distributions will facilitate deep lung deposition of the bioactive agent whether administered using a dry powder inhaler (DPI), metered-dose inhaler (MDI), or

nebulizer [0126]. Tarara defines fine particle fraction (FPF) as "the percentage of the total amount of active medicament delivered per actuation from the mouthpiece of a DPI, MDI or nebulizer onto plates 2-7 of an 8 stage Andersen cascade impactor." Tarara's formulations preferably have a **fine particle fraction of approximately 20% or more by weight of the perforated microstructures** (w/w), even more preferably **from about 30 to 70% w/w**. In selected embodiments the present invention will preferably comprise a **fine particle fraction of greater than about 30%, 40%, 50%, 60%, 70% or 80% by weight** [0127].

Tarara states that skilled artisans would appreciate that the perforated microstructures of his invention are useful in DPIs used in inhalation therapies [0131]. Currently, the range of dry powder that can be filled into a unit dose container is from 5 to 15 mg, corresponding to a drug **loading ranging from 25 to 500 micrograms per dose (i.e. actuation)** and bulk reservoir type DPIs can meter between 200 micrograms to 20 mg of powder per actuation [0132].

Tarara discloses that stabilized dispersions of his invented pharmaceutical formulations are particularly suitable for the pulmonary administration of bioactive agents (e.g. adrenaline), which may be used for the **localized or systemic administration of compounds** to any location of the body [0186].

Applicant's attention is drawn to Examples X-XII, wherein Tarara discloses the preparation of various pharmaceutical particles comprising active agents, surfactant, and lactose excipient (Example XI), having **a tap density less than 0.1 g/cm$^3$**. Surfactants are excipients as well. The Examiner would also like to draw the Applicant's attention to Figure 5 in which Tarara discloses the distribution of an exemplary particulate composition in an Anderson cascade impactor as delivered by a DPI and a MDI. It is well known in the art that the different stages of

the Anderson cascade impactor correlate to the delivery of particles to different regions of the pulmonary system, with stages 6-7 corresponding to delivery of particles to the deep lung (i.e. alveolar region of the pulmonary system). See for example, Radhakrishnan (U.S. Patent No. 5,192,528), where the correlation of the different stages of the Anderson cascade impactor with different regions of the pulmonary system is described.

Slutsky teaches a breath activated inhaler, which may contain a single dose of a powdered medicament, which is intended to be inhaled by the patient in a single breath (title; abstract; col. 4, lines 47-49; col. 6, lines 27-62; col. 8, lines 50-55 and 60-62; col. 9, lines 25-30; col. 10, line 48 through col. 13, line 42, especially col. 12, lines 38-59). Slutsky teaches an alternative breath-activated inhaler capable of delivering a large dose of powdered medicament in a single breath (col. 12, lines 38-59).

***Ascertainment of the Difference Between Scope the Prior Art and the Claims (MPEP §2141.012)***

Tarara lacks the explicit teaching that powdered formulations are delivered in a single breath actuated step. This deficiency is cured by the teachings of Slutsky.

***Finding of Prima Facie Obviousness Rational and Motivation (MPEP §2142-2143)***

It would have been *prima facie* obvious to a person of ordinary skill at the time of the instant invention to combine the teachings of Tarara and Slutsky, because Tarara teaches powdered pharmaceutical formulations for inhalation administration and Slutsky teaches breath-activated inhalers for the administration of powdered medicaments. It would also have been

obvious to combine the teachings of Tarara and Slutsky, because as taught by Slutsky, use of Slutsky's invented inhaler would allow one to deliver a large dose in a single breath. An ordinary skilled artisan would have been motivated to utilize an inhaler capable of delivering a therapeutically effective dose in a single breath, because this would clearly improve patient compliance. Patient compliance would clearly be improved, because one would need fewer administrations to deliver a therapeutically effective dose contained in an inhaler. Regarding the amount of epinephrine delivered, Applicants' claims have no maximum limit on the amount of epinephrine delivered, merely that at least 50 micrograms is delivered. The combination of Tarara's invented compositions with Slutsky's invented inhaler would reasonably be expected to deliver at least 50 micrograms of epinephrine, because one can modify the dosage of epinephrine present in an inhaler to ensure the delivery of a therapeutically effective amount of epinephrine and Slutsky's inhaler permits delivery of an entire dose in a single breath. Therefore, an ordinary skilled artisan would have had a reasonable expectation of success upon combination of the prior art teachings. Therefore, the claimed invention, as a whole, would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, because the combined teachings of the prior art is fairly suggestive of the claimed invention.

***Response to Arguments***

Applicant's arguments filed 11/27/07 have been fully considered but they are not persuasive. Applicants traverse the instant rejection by arguing: (1) the rejection is allegedly improper because an explicit motivation to administer epinephrine by inhalation is not disclosed in Tarara; (2) an ordinary skilled artisan would allegedly not be motivated to administer epinephrine via inhalation to a person in need of epinephrine, a life saving drug, in a crisis

situation that also involved difficulty breathing; (3) it is allegedly only through improper hindsight that an ordinary skilled artisan would have been motivated to administer epinephrine via inhalation; (4) Slutsky allegedly teaches away from Applicants' claimed method of treatment, because in one embodiment Slutsky teaches to restrict air flow to better administer nicotine.

The Examiner respectfully disagrees with Applicants' traversal arguments. Regarding (1), as Applicants are well aware, the Supreme Court has stated that a reference is not required to provide an explicit or implicit motivation to show obviousness. Obviousness can properly be demonstrated based upon what is well known in the art, such as, the fact that epinephrine is indicated for treating various conditions and can suitably be administered by inhalation (KSR Intl. Col. V. Teleflex Inc. 127 S. Ct. 1727, 1742, 82 USPQ2d 1385, 1398 (2007)). See, for example, the 1993 Drug Information Handbook ("DIH"), pp 323, which is already of record[1], for evidence that the inhalation administration of epinephrine is well known. The "DIH" has been referred to herein to address Applicants' arguments. Regarding (2), Applicants' claims do not specify any condition that is being treated. Applicants' arguments imply that epinephrine is only administered in "crisis situations" in which the life of the person receiving treatment is mortally at risk. However, Applicants' claims do not recite this limitation. As evidenced by the teachings of the "DIH," epinephrine is known for the treatment of open angle (chronic simple) glaucoma. Glaucoma clearly is not a "life threatening" crisis situation. In response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., administration in life-threatening crisis situations that also involve difficulty breathing) are not recited in the rejected claim(s). Although the claims are

[1] The 1993 DIH was cited in the office action mailed on April 6, 2006.

interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). Regarding (3), In response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971). Regarding (4), Applicants claims do not require any specific air flow or specify that the person receiving the epinephrine is having difficulty breathing. Furthermore, as Applicants are aware, epinephrine is a well-known drug, that can suitably be administered by inhalation (See DIH, supra). Finally, Applicants' data is noted. Applicants' data does not demonstrate any unexpected results, and merely confirms that inhalation administration of epinephrine results in pharmacokinetic observations comparable to systemic administration of epinephrine by injection. Thus, the instant rejection is deemed to remain proper.

The rejection of claims 161-162 under 35 U.S.C. 103(a) as being unpatentable over Tarara et al. (US 2005/0074498) in view of Slutsky et al. (U.S. Patent No. 6,102,036) as applied to claims 140-144, 153, and 156-160 above, and further in view of Physicians' Desk Reference (PDR, page 1236) (already of record) **is maintained** for the reasons of record, which are restated below for Applicants' convenience, and further articulated below.

***Applicant Claims***

Applicants claim a method as described above in the instant office action wherein epinephrine is administered to treat anaphylaxis, edema, bronchoconstriction, bronchospasm, and airway constriction.

***Determination of the Scope and Content of the Prior Art (MPEP §2141.01)***

The teachings of Tarara were set forth on pages 3-5 of the office action mailed on April 6, 2006 and have been restated above in the instant office action. The teachings of the PDR were set forth on page 7 of the office action mailed on April 6, 2006 mailed and are restated herein below in the instant office action. The teachings of Slutsky were set forth in the office action mailed on August 7, 2007 and have been restated above in the instant office action.

The 2002 PDR teaches on page 1236 that **epinephrine is essential in the treatment of anaphylaxis** (1st sentence in the section entitled "Precautions"). It also teaches in the "Clinical Pharmacology" section that epinephrine acts to relieve vasodilation and increased vascular permeability. It also **relaxes the bronchial smooth muscles**, which alleviates wheezing and dyspnea. Other conditions alleviated by administration of epinephrine are pruritis, urticaria, and **angioedema** and it may be effective in relieving gastrointestinal and genitourinary symptoms associated with anaphylaxis.

***Ascertainment of the Difference Between Scope the Prior Art and the Claims (MPEP §2141.012)***

Tarara lacks the teaching of a method of treatment wherein epinephrine is administered to treat anaphylaxis, edema, bronchoconstriction, bronchospasm, and airway constriction. This deficiency is cured by the teachings of the PDR.

***Finding of Prima Facie Obviousness Rational and Motivation (MPEP §2142-2143)***

It would have been obvious to a person of ordinary skill in the art at the time of the instant invention to combine the teachings of Tarara/Slutsky and the PDR, because Tarara teaches pharmaceutical preparations wherein the perforated microstructures may comprise adrenaline (i.e. epinephrine) active agent and the PDR describes known treatments which utilize epinephrine to treat anaphylaxis, angioedema, and relax the bronchial smooth muscles. A skilled artisan would have been motivated to combine the prior art references, because the PDR is a well-known medical reference consulted by physicians and other medical professionals to determine which medicaments are appropriate to treat which conditions or disorders. A person of ordinary skill in the art would have had a reasonable expectation of success upon combination of the prior art references, because Tarara teaches pharmaceutical compositions comprising adrenaline and the PDR teaches treatments in which the administration of adrenaline is appropriate, such as in the treatment of anaphylaxis, bronchoconstriction, bronchospasm, etc.

Therefore, the claimed invention, as a whole, would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, because the combined teachings of the prior art is fairly suggestive of the claimed invention.

***Response to Arguments***

Applicant's arguments filed 11/27/07 have been fully considered but they are not persuasive. Applicants traverse the instant rejection by arguing that although the PDR establishes that it was well known to delivery epinephrine to treat anaphylaxis, bronchoconstriction, bronchospasm, airway constriction, and edema it is allegedly unobvious to administer epinephrine by inhalation.

The Examiner respectfully disagrees with Applicants traversal argument, because, as has been demonstrated above in the instant office action, on the record, and conceded by Applicants, epinephrine is well known for the treatment of anaphylaxis, bronchoconstriction, bronchospasm, airway constriction, and edema. Administration of epinephrine to treat a condition for which it is indicated for is prima facie obvious. It is noted that epinephrine is a well-known betamimetic, which are known to have bronchodilating effects. Betamimetics are routinely administered to treat asthma and other respiratory diseases characterized by bronchoconstriction, for example. Thus, there is no reason to conclude that epinephrine could not successfully be administered by inhalation. Furthermore, the inhalation administration of epinephrine is well known (See the 1993 edition of the DIH discussed above and already of record. The "DIH" has been referred to herein merely to further address Applicants' arguments. Therefore, the claimed invention, as a whole, would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, because the combined teachings of the prior art is fairly suggestive of the claimed invention.

Claims 140-143, 146-150, 159, 160, and 162 under 35 U.S.C. 103(a) as being unpatentable over Foster et al. (US 2003/0215512) in view of Tarara et al. (US 2005/0074498) and Slutsky (U.S. Patent No. 6,102,036) **is maintained** for the reasons of record, which are restated below for Applicants' convenience, and further articulated below.

***Applicant Claims***

Applicants claim a method as described above in the instant office action.

***Determination of the Scope and Content of the Prior Art (MPEP §2141.01)***

The teachings of Tarara were set forth on pages 3-5 of the office action mailed on April 6, 2006 and have been restated above in the instant office action. The teachings of Slutsky were set forth in the office action mailed on August 7, 2007 and have been restated above in the instant office action. The teachings of Foster were set forth on pages 8-10 of the office action mailed on April 6, 2006 and are restated below in the instant office action.

Foster teaches a composition that comprises a mixture of a pharmaceutically acceptable glassy matrix and at least one pharmacologically active material within the glassy matrix. It may be further mixed with a powdered, pharmaceutically acceptable carrier (abstract).

Foster teaches that the powdered composition will be composed of **particles** having a mass median diameter (MMD) of about 1-5 microns and a mass median aerodynamic diameter **(MMAD) of about 1-5 microns** [0051]. The active materials in the composition are active drug substances preferably used for administration via pulmonary inhalation. The unit dosage typically will be between 0.25 mg and 15 mg of total material in the dry powder, wherein the

active will comprise **about 0.05% to about 99.0% by weight** of the composition [0054]. In the dry state the drug or phase containing the active **may be either crystalline or amorphous in form** [0055]. Active small molecules for **systemic and local lung applications** for use in Foster's compositions include steroids and bronchodilators, including **adrenaline** [0056]. Systemic diseases treatable using Foster's compositions are taught in [0060] and pulmonary diseases, which are suitable targets for treatment include, chronic bronchitis, asthma, ARD, COPD, **bronchospasm**, and bronchial asthma [0061]. In addition to the glass former, the composition may contain other additives (i.e. excipients) [0064], including non-polar amino acids (e.g. **leucine**) [0068]. The glass former may be used alone or **in combination with additives, which may be crystalline or amorphous** [0064]. Suitable glass formers include organic carboxylic salts and the most preferable glass formers include **sodium tartrate, lactose, etc.** [0071] to [0072]. In Examples 15-16, Foster teaches exemplary formulations comprising a small molecule active (albuterol). The Tables in [0232] and [0234] obviously disclose a FPF in the column with the heading "% particle mass < 5 microns in size."

***Ascertainment of the Difference Between Scope the Prior Art and the Claims (MPEP §2141.012)***

Foster lacks the teaching of compositions having a tap density of less than 0.4 g/cm$^3$, which is cured by the teachings of Tarara. Foster lacks the teaching of administration in a single breath-activated step. This deficiency is cured by the teachings of Slutsky.

***Finding of Prima Facie Obviousness Rational and Motivation (MPEP §2142-2143)***

It would have been obvious to a person of ordinary skill in the art at the time of the instant application to combine the teachings of Foster and Tarara/Slutsky, because all inventors teach compositions suitable for inhalation pulmonary administration of active agents. A skilled artisan would have been motivated to combine the teachings of Foster and Tarara, because Tarara's compositions provide teachings of desirable physical characteristics of acrodynamically light particles especially suitable for inhalation administration. An ordinary skilled artisan cognizant of the teachings of Slutsky would be motivated to utilize Slutsky's breath-activated inhaler to improve patient compliance and facilitate delivery of a particulate pharmaceutical formulation in the fewest number of administrations. A skilled artisan would have had a reasonable expectation of success upon combination both Tarara and Foster teach adrenaline-containing (i.e. epinephrine) compositions designed for inhalation pulmonary administration. Therefore, the claimed invention, as a whole, would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, because the combined teachings of the prior art is fairly suggestive of the claimed invention.

***Response to Arguments***

Applicant's arguments filed 11/27/07 have been fully considered but they are not persuasive. Applicants traverse the instant rejection by arguing: (1) the Examiner has allegedly continued to ignore claim limitations; (2) motivation to combine the cited references has allegedly not been provided; (3) the cited combination of references does not teach the inhalation administration in a single breath-activated step the delivery of epinephrine to a person likely to

be in severe respiratory distress; and (4) an Slutsky allegedly teaches away from the claimed method.

The Examiner respectfully disagrees with Applicants traversal arguments. Regarding (1), it is unclear which limitations have allegedly been ignored by the Examiner. All limitations have been properly addressed. Applicants may disagree with the conclusion of prima facie obviousness, but this does not demonstrate that the claim limitations have been blatantly ignored as implied by Applicants. Regarding (2), a motivation was clearly articulated on the record and has been restated above, specifically,

"An ordinary skilled artisan cognizant of the teachings of Slutsky would be motivated to utilize Slutsky's breath-activated inhaler to improve patient compliance and facilitate delivery of a particulate pharmaceutical formulation in the fewest number of administrations."

Regarding (3), the combined references teach the administration of epinephrine to treat bronchospasm. Furthermore, epinephrine is a well-known bronchodilator. Bronchodilation is well known in the art to counteract bronchoconstriction that is often the cause of difficulty breathing. Furthermore, concerning claims 140-143, 146-150, 159, and 160, these claims do not recite that the patient receiving treatment is suffering from severe respiratory distress. In response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., the person in need of epinephrine is suffering from severe respiratory distress) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). Regarding (4), the Examiner respectfully disagrees. Applicants' claims do not require

any specific flow rate and as has continually been reiterated on the record, epinephrine is well-known for the treatment of conditions, including bronchospasm. Thus, it is prima facie obvious to administer a known compound to treat a condition for which it is indicated.

The rejection of claim 171 under 35 U.S.C. 103(a) as being unpatentable over Tarara et al. (US 2005/0074498) in view of Slutsky et al. (U.S. Patent No. 6,102,036) as applied to claims 140-144, 153, and 156-160 above, and further in view of Radhakrishnan (U.S. patent 5,049,389) (already of record) **is maintained** for the reasons of record and further articulated below.

***Applicant Claims***

Applicants claim a method as described above in the instant office action.

***Determination of the Scope and Content of the Prior Art (MPEP §2141.01)***

The teachings of Tarara were set forth on pages 3-5 of the office action mailed on April 6, 2006 and have been restated above in the instant office action. The teachings of Slutsky were set forth in the office action mailed on August 7, 2007 and have been restated above in the instant office action. The teachings of Radhakrishnan were set forth on page 10 of the office action mailed on April 6, 2006 and are restated below in the instant office action.

Radhakrishnan teaches a **method for treating a patient in need of epinephrine** by administration of particles comprising a nonphospholipid composition consisting essentially of nonphospholipid components and a drug (adrenaline) aerosolized into aerosol particles having a

**mass median aerodynamic diameter smaller than 2.1 □m** and providing a **slow or sustained release of the drug in the lungs** (claims 13 and 15).

Radhakrishnan teaches that the dried particle liposome formulation in the form of dry powder can be prepared either by lyophilization or spray drying.

Radhakrishnan teaches that the method of treating a patient is by the **inhalation route of administration** to a person in need of such treatment (claims 13, 18, and 20).

Radhakrishnan discloses **that drug crystallization does not occur outside or inside the liposomes**, nor does sedimentation occur from the suspension (column 13, lines 62-67).

***Ascertainment of the Difference Between Scope the Prior Art and the Claims (MPEP §2141.012)***

Tarara lacks the teaching of compositions releasing active agents in a sustained manner, which is cured by the teachings of Radhakrishnan.

***Finding of Prima Facie Obviousness Rational and Motivation (MPEP §2142-2143)***

It would have been obvious to a person of ordinary skill in the art at the time of the instant invention to combine the teachings of Tarara and Radhakrishnan, because both inventors teach particulate compositions comprising epinephrine, which is intended for inhalation administration. A skilled artisan would have been motivated to combine the teachings of Tarara and Radhakrishnan to obtain sustained release compositions wherein the active drug and excipients do not crystallize within the liposome and which do not undergo sedimentation when

suspended. A person of ordinary skill at the time of the instant invention would have had a reasonable expectation of success upon combination of the prior art references, because both inventors teach particular compositions for inhalation comprising adrenaline. Therefore, the claimed invention, as a whole, would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, because the combined teachings of the prior art is fairly suggestive of the claimed invention.

***Response to Arguments***

Applicant's arguments filed 11/27/07 have been fully considered but they are not persuasive. Applicants traverse the instant rejection by arguing: (1) neither Tarara nor Radhakrishnan teach "particular" compositions for inhalation comprising adrenaline (i.e. these references do not teach anticipatory adrenaline compositions; (2) Radhakrishnan addresses a problem encountered with liquid-based nebulizers that is different than the problem addressed by Applicants.

The Examiner respectfully disagrees with Applicants traversal arguments. Regarding (1), this rejection seems off point, because the instant rejection is based upon a conclusion of obviousness not anticipation. Regarding (2), the prior art is not required to address the same problem that motivated Applicants claimed invented method. Furthermore, an ordinary skilled artisan would realize that the use of liposomes would provide for the sustained release of epinephrine upon inhalation administration, as is taught by Radhakrishnan. It is also noted that an ordinary skilled artisan would also be cognizant that the liquid from the Radhakrishnan formulations could be evaporated to obtain powdered liposomes, which would reasonably be

expected to exhibit the sustained release properties in vivo after inhalation administration. Therefore, the claimed invention, as a whole, would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, because the combined teachings of the prior art is fairly suggestive of the claimed invention.

The rejection of claims 163-170 under 35 U.S.C. 103(a) as being unpatentable over Tarara et al. (US 2005/0074498) in view of Slutsky et al. (U.S. Patent No. 6,102,036) as applied to claims 140-144, 153, and 156-160 above, and further in view of Warren et al. (*Clin. Pharmacol. Ther.*, 1986, *40(6)*, 673-678) (already of record) **is maintained** for the reasons of record restated and further articulated below.

***Applicant Claims***

Applicants claim a method as described above in the instant office action.

***Determination of the Scope and Content of the Prior Art (MPEP §2141.01)***

The teachings of Tarara were set forth on pages 3-5 of the office action mailed on April 6, 2006 and have been restated above in the instant office action. The teachings of Slutsky were set forth in the office action mailed on August 7, 2007 and have been restated above in the instant office action. The teachings of Warren were set forth on pages 11-12 of the office action mailed on April 6, 2006 and are restated below in the instant office action.

Warren et al. teach that inhalation of 30 puffs of adrenaline (3 mg) from a pressurized aerosol resulted in peak blood plasma levels of adrenaline **($C_{max}$) of 4.22 ± 1.93 nM after 1**

**minute ($T_{max}$) of administration.** They compared these results to adrenaline administered by a subcutaneous injection, which resulted in peak blood plasma levels of adrenaline **($C_{max}$) of 2.43 ± 0.47 nM after 10 minutes ($T_{max}$) of administration**. The blood plasma levels of adrenaline were used as a measure of the systemic absorption of adrenaline (abstract, Figures 1 and 3 on pages 674 and 675, respectively).

***Ascertainment of the Difference Between Scope the Prior Art and the Claims (MPEP §2141.012)***

Tarara lacks the express teaching of Cmax and Tmax of different administration routes, specifically inhalation administration vs. non-intravenous injection.

***Finding of Prima Facie Obviousness Rational and Motivation (MPEP §2142-2143)***

A person of ordinary skill in the art at the time of the instant invention would have been able to obtain information on Warren et al.'s studies showing that the administration of inhaled adrenaline would lead to a shorter time for adrenaline blood plasma levels to reach a maximum concentration as a predictor of what one would expect upon inhalation administration of Tarara's pharmaceutical formulations. A skilled artisan would have known that drug blood plasma levels are a measure of the systemic absorption of a pharmaceutical agent and that said agent would therefore be acting systemically. Based on Warren's data, a person of ordinary skill in the art at the time of the instant invention would have been motivated to administer epinephrine to a patient and would have had a reasonable expectation that said drug administered by inhalation would result in maximal adrenaline blood serum levels in a shorter period of time when

compared to non-intravenous injection routes of administration. Therefore, the claimed invention, as a whole, would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, because the combined teachings of the prior art is fairly suggestive of the claimed invention.

***Response to Arguments***

Applicant's arguments filed 11/27/07 have been fully considered but they are not persuasive. Applicants traverse the instant rejection by attacking Warren individually and reiterating the arguments traversing the rejection of claim 140 that have been discussed and rebutted supra. In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

The rejection of claims 172-173 under 35 U.S.C. 103(a) as being unpatentable over Foster et al. (US 2003/0215512) in view of Tarara et al. (US 2005/0074498) and Slutsky (U.S. Patent No. 6,102,036) as applied to claims 140-143, 146-150, 159, 160, and 162 above, in further view of the *Drug Information Handbook* (1993) ("DIH") **is maintained** for the reasons of record restated and further articulated below.

***Applicant Claims***

Applicants claim a method as described above in the instant office action.

***Determination of the Scope and Content of the Prior Art (MPEP §2141.01)***

The teachings of Tarara were set forth on pages 3-5 of the office action mailed on April 6, 2006 and have been restated above in the instant office action. The teachings of Slutsky were set forth in the office action mailed on August 7, 2007 and have been restated above in the instant office action. The teachings of the DIH were set forth on page 12 of the office action mailed on April 6, 2006 and are restated below in the instant office action.

The use of epinephrine bitartrate would have been readily apparent to a skilled artisan, because it is one of the most common salts of epinephrine employed in pharmaceutical formulations (*Drug Information Handbook*, Lexi-Comp, Inc.: Cleveland, OH, 1993, pp 322-325).

***Ascertainment of the Difference Between Scope the Prior Art and the Claims (MPEP §2141.012)***

Tarara lacks the express teaching of the teaching of a composition comprising epinephrine bitartrate.

***Finding of Prima Facie Obviousness Rational and Motivation (MPEP §2142-2143)***

It would have been obvious to a person of ordinary skill in the art to combine the teachings of Tarara/Foster with the DIH, because the DIH is a standard reference used in the pharmaceutical art and the other two prior art references teach pharmaceutical compositions comprising epinephrine. A skilled artisan would have been motivated to combine the teachings of the DIH with those of Tarara and Foster, because epinephrine is a known active agent and

epinephrine bitartrate is a common salt of said active used in commercially available pharmaceutical formulations. A person of ordinary skill in the art would have had a reasonable expectation of success upon combination of the prior art references, because Tarara, Foster, and the DIH teach compositions wherein the active is epinephrine, and the bitartrate salt of adrenaline is commonly used in pharmaceutical formulations. Regarding the amount of active agent, Foster teaches an overlapping range for the amount (i.e. about 0.05% to about 99.0% by w/w). In addition, it would have been readily apparent to a skilled artisan per the teachings of Foster that the remainder of the composition would comprise glass-forming excipient (i.e. sodium tartrate) and other additives (e.g. leucine). The amount of a specific ingredient in a composition is clearly a result effective parameter that a person of ordinary skill in the art would routinely optimize. Optimization of parameters is a routine practice that would be obvious for a person of ordinary skill in the art to employ. It would have been customary for an artisan of ordinary skill to determine the optimal amount of each ingredient needed to achieve the desired results. Thus, absent some demonstration of unexpected results from the claimed parameters, the optimization of ingredient amounts would have been obvious at the time of applicant's invention. Therefore, the claimed invention, as a whole, would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, because the combined teachings of the prior art is fairly suggestive of the claimed invention.

***Response to Arguments***

Applicant's arguments filed 11/27/07 have been fully considered but they are not persuasive. Applicants traverse the instant rejection by arguing that (1) the teachings of Foster

and Tarara do not provide a reasonable expectation of success of mixing epinephrine, leucine, and sodium tartrate in specific amounts to obtain a composition; (2) Foster and Tarara allegedly are deficient because these references do not disclose or suggest the desirability of obtaining Applicants' claimed compositions; (3) the mere fact that both Tarara and Foster teach particulate formulations, which may contain adrenaline is an insufficient motivation to combine references .

The Examiner respectfully disagrees with Applicants' traversal arguments. Applicants' formulations comprise epinephrine in the form of a conventionally administered epinephrine salt (epinephrine bitartrate) that is well known in the art (DIH). The disclosure of a broad range of active agent in Foster's compositions is an invitation to an ordinary skilled artisan to optimize the amount of a particular active agent to find the optimal amount of said active suitable for the artisan's intended use of said composition. Upon determination of the optimum amount of epinephrine in a particulate formulation it would have been well within the skill of the ordinary artisan to vary the amount of the other conventional additives needed to obtain a composition exhibiting desirable properties. Regarding (1), Applicants arguments are unpersuasive, because there is no reason of record that an ordinary skilled artisan would not have an expectation of successfully mixing a well known active agent (i.e. epinephrine bitartrate) in particulate form with other well known and conventional particulate excipients (i.e. sodium tartrate and leucine). An ordinary skilled artisan would not conclude that one could not mix epinephrine bitartrate, sodium tartrate, and leucine, because all these components are taught by the prior art. Regarding (2), Applicants have not demonstrated any particular criticality of the particular components mixed in the recited amounts. Rather, mixing epinephrine, taught as being suitable for the preparation of inhalable dry powders, with excipients taught in the prior art

as also being suitable for the preparation of particulate compositions is well within the capability of the ordinary skilled artisan and would have a reasonable expectation of success, absent evidence to the contrary. Therefore, the claimed invention, as a whole, would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, because the combined teachings of the prior art is fairly suggestive of the claimed invention.

***Double Patenting***

A rejection based on double patenting of the "same invention" type finds its support in the language of 35 U.S.C. 101 which states that "whoever invents or discovers any new and useful process ... may obtain a patent therefor ..." (Emphasis added). Thus, the term "same invention," in this context, means an invention drawn to identical subject matter. See *Miller v. Eagle Mfg. Co.*, 151 U.S. 186 (1894); *In re Ockert*, 245 F.2d 467, 114 USPQ 330 (CCPA 1957); and *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970).

A statutory type (35 U.S.C. 101) double patenting rejection can be overcome by canceling or amending the conflicting claims so they are no longer coextensive in scope. The filing of a terminal disclaimer cannot overcome a double patenting rejection based upon 35 U.S.C. 101.

Applicant is advised that should claim140 be found allowable, claim 144 will be objected to under 37 CFR 1.75 as being a substantial duplicate thereof. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k). In paragraph [0120] of Applicants' specification the term "aerodynamically light" is defined as referring to particles having a tap density of less than 0.4 $g/cm^3$ (see below). Claim 140 recites that the particles administered have a tap density less than 0.4 $g/cm^3$; thus, these particles are aerodynamically light per Applicants' definition.

Detail Description Paragraph - DETX (99):

[0120] In a preferred embodiment of the invention, particles administered to a subject's respiratory system have a tap density of less than about 0.4 g/cm.sup.3. Particles having a tap density of less than about 0.4 g/cm.sup.3 are referred to herein as "aerodynamically light." In other preferred embodiments, the particles have a tap density less than or equal to about 0.3 g/cm.sup.3 or less than or equal to about 0.2 g/cm.sup.3. In other embodiments, the particles have a tap density less than or equal to about 0.1 g/cm.sup.3, or less than or equal to about 0.05 g/cm.sup.3. Tap density is a measure of the envelope mass density characterizing a particle. The envelope mass density of a particle of a statistically isotropic shape is defined as the mass of the particle divided by the minimum sphere envelope volume within which it can be enclosed. Features which can contribute to low tap density include irregular surface texture and porous structure.

## *Conclusion*

**Claims 140-144, 146-150, 153, and 156-173 are rejected. Claims 161-162 are objected. No claims are allowed.**

Any inquiry concerning this communication or earlier communications from the examiner should be directed to James H. Alstrum-Acevedo whose telephone number is (571) 272-5548. The examiner can normally be reached on M-F, 9:00-6:30, with every other Friday off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Johann Richter can be reached on (571) 272-0646. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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